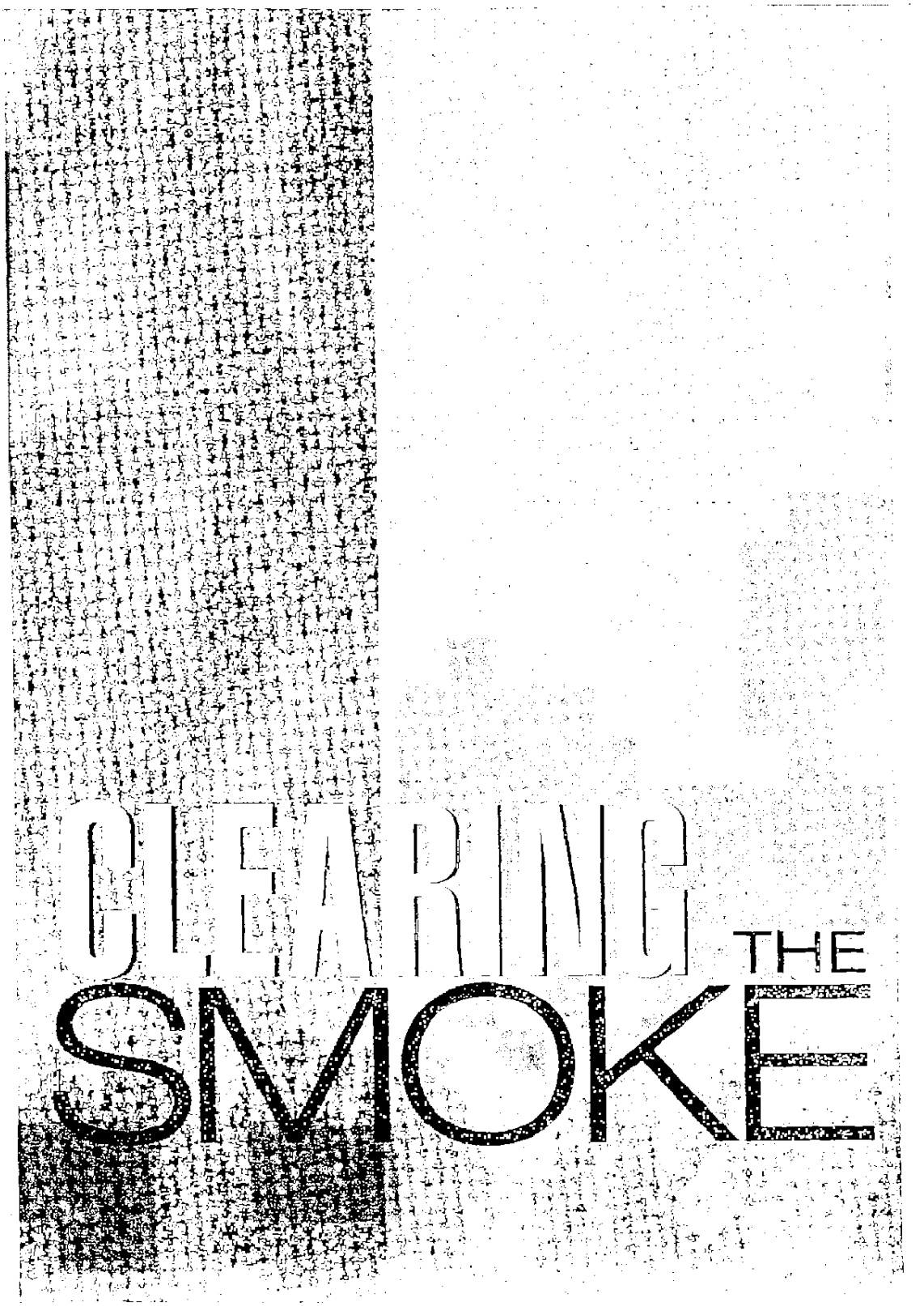
ADVANCE COPY



PM3006856906

Clearing the Smoke

Assessing the Science Base for Tobacco Harm Reduction

Kathleen Stratton, Padma Shetty, Robert Wallace, and
Stuart Bondurant, Editors

Committee to Assess the Science Base for Tobacco Harm Reduction

Board on Health Promotion and Disease Prevention

INSTITUTE OF MEDICINE

NATIONAL ACADEMY PRESS
Washington, D.C.

NATIONAL ACADEMY PRESS • 2101 Constitution Avenue, N.W. • Washington, DC 20418

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

Support for this project was provided by the Food and Drug Administration prior to the March 2000 decision by the Supreme Court denying FDA comprehensive authority over tobacco products. The views presented in this report are those of the Institute of Medicine Committee to Assess the Science Base for Tobacco Harm Reduction and are not necessarily those of the funding agencies.

Additional copies of this report are available for sale from the National Academy Press, 2101 Constitution Avenue, N.W., Box 285, Washington, DC 20055. Call (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area), or visit the NAP's home page at **www.nap.edu.** The full text of this report is available at **www.nap.edu.**

For more information about the Institute of Medicine, visit the IOM home page at **www.iom.edu.**

Printed in the United States of America.

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

"Knowing is not enough; we must apply.
Willing is not enough; we must do.
—Goethe

INSTITUTE OF MEDICINE

Shaping the Future for Health

PM3006856909

THE NATIONAL ACADEMIES

National Academy of Sciences
National Academy of Engineering
Institute of Medicine
National Research Council

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Bruce M. Alberts is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. William A. Wulf is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Kenneth I. Shine is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Bruce M. Alberts and Dr. William A. Wulf are chairman and vice chairman, respectively, of the National Research Council.

COMMITTEE TO ASSESS THE SCIENCE BASE FOR TOBACCO HARM REDUCTION

STUART BONDURANT, M.D. (*Chair*), Professor, Department of Medicine, University of North Carolina, Chapel Hill

ROBERT WALLACE, M.D., M.Sc., *(Vice-Chair)* Professor, Department of Epidemiology and Internal Medicine, University of Iowa Colleges of Public Health and Medicine

J. RICHARD CROUT, M.D., President, Crout Consulting

GARRET FITZGERALD, M.D., Professor and Chair, Department of Pharmacology, University of Pennsylvania

ADI GAZDAR, M.D., Professor, Department of Pathology, University of Texas Southwestern Medical Center

GARY GIOVINO, Ph.D., M.S., Senior Research Scientist, Roswell Park Cancer Institute

DOROTHY HATSUKAMI, Ph.D. Professor, Department of Psychiatry and Psychology, University of Minnesota

ROGENE F. HENDERSON, Ph.D., Senior Biochemist/Toxicologist, Lovelace Respiratory Research Institute

PETER REUTER, Ph.D., Professor, School of Public Affairs and Department of Criminology, University of Maryland

DAVID J. RILEY, M.D., Professor of Medicine, Division of Pulmonary and Critical Care Medicine, University of Medicine and Dentistry of New Jersey – Robert Wood Johnson Medical School

PETER SHIELDS, M.D., Professor and Chief, Cancer Genetics and Epidemiology Program, Lombardi Cancer Center, Georgetown University Medical Center

JAMES WILLERSON, M.D., Professor and Chair of Internal Medicine, University of Texas Medical School

Health Promotion and Disease Prevention Board Liaison

KENNETH E. WARNER, Ph.D., Professor, Department of Health Management and Policy, School of Public Health, University of Michigan

Neuroscience and Behavioral Health Board Liaison

RICHARD J. BONNIE, L.L.B., John S. Battle Professor of Law, Director, Institute of Law, Psychiatry, and Public Policy, University of Virginia School of Law

Consultants

NEAL BENOWITZ, M.D., Professor and Chief of the Division of Clinical Pharmacology, Departments of Medicine, Biopharmaceutical Sciences, and Psychiatry; University of California, San Francisco

CHRISTOPHER LOFFREDO, M.S. Ph.D., Assistant Professor, Lombardi Cancer Center, Georgetown University Medical Center

Staff

KATHLEEN STRATTON, Ph.D., Study Director
PADMA SHETTY, M.D., Program Officer
ANN ST. CLAIRE, Senior Project Assistant
ROSE MARIE MARTINEZ, Sc.D., Director, Board on Health Promotion and Disease Prevention
TERRY PELLMAR, Ph.D., Director, Division of Neuroscience and Behavioral Health

REVIEWERS

The report was reviewed by individuals chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments to assist the authors and the Institute of Medicine in making the published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The content of the review comments and the draft manuscript remain confidential to protect the integrity of the deliberative process. The committee wishes to thank the following individuals for their participation in the report review process:

Daniel Azarnoff, D.L. Azarnoff Associates
Alfred Fishman, University of Pennsylvania
Margaret Gilhooley, Seton Hall University
Jack Henningfield, Pinney Associates
Peter Barton Hutt, Covington and Burling
Roger McClellan, Chemical Industry Institute of Toxicology, President Emeritus
Patricia Dolan Mullen, University of Texas
Peter Nowell, University of Pennsylvania
William Parmley, University of California, San Francisco
Thomas Pearson, University of Rochester
Frederica Perera, Columbia University
John Pierce, University of California, San Diego
Stephen Rennard, University of Nebraska
Joseph Rodricks, The Life Sciences Consultancy
Jonathan Samet, Johns Hopkins University
Thomas Schelling, University of Maryland
John Slade, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School
Judith Wilkenfeld, Campaign for Tobacco Free Kids
Gerald Wogan, Massachusetts Institute of Technology
Raymond Woosley, Georgetown University

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **David Challoner**, (review monitor) University of Florida and **Hugh Tilson**, (review coordinator) University of North Carolina. Appointed by the National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

Tobacco has been used by humans for at least a millennium, and its harmful effects have been suspected for at least 200 years. In the last 50 years, convincing and generally accepted evidence has established the fact that exposure to tobacco products is the major single cause of early human mortality and morbidity in developed nations and in many developing nations as well.

Even nonsmokers suffer morbidity and excess mortality from the toxic effects of inhalation of sidestream smoke. Both smokers and their nonsmoking associates are more likely to be injured in fires and automobile accidents. The personal and social price we pay for establishing and sustaining nicotine addiction through exposure to tobacco smoke is our greatest controllable health cost and one of our greatest social burdens.

It has been scientifically established that reduced exposure to tobacco smoke by lifelong abstinence and avoidance of smoke eliminates the added risk and harm and that cessation, even after many years of smoking, reduces risk and harm both immediately and in the long term for many tobacco-related conditions.

Several smoking cessation programs, some aimed at individuals and some at communities, have been shown to be modestly effective in assisting smokers to quit smoking. These programs have been shown to be more effective with the added use of nicotine replacement by patches for absorption through the skin, by nicotine-containing chewing gum or sprays for absorption through oral or nasal mucous membranes, or by the administration of psychotropic drugs to reduce the desire for nicotine.

However, with the most intensive application of the most effective known programs for prevention and cessation, approximately 10-15% of the adults in the United States are expected to be regular users of tobacco in 2010, and they will continue to suffer the increased incidence of harmful and lethal consequences. Among this group are many who cannot or will not stop using tobacco, and it is to this group that effective programs and products of harm reduction should be directed.

New tobacco products and nicotine replacement products are being marketed frequently and, along with products now on the market, often have associated direct or implied health claims. Some of the new products differ from traditional products in ways that appear minor, whereas others involve substantial changes in types of tobacco, in additives, or in curing, blending, or processing of the tobacco. New products may also change the composition of the aerosol the consumer inhales compared to cigarette smoke by changing the burning temperature of the tobacco by new methods of combustion, by limiting the release of smoke into the atmosphere, by dilution of the smoke with air, and/or by adding unnatural carriers for smoke particles.

Although many components of tobacco are known to be toxic, little is known of the specific dose-response relations of the individual toxins as they occur in cigarette smoke or of the interactions between the constituents of tobacco smoke. There is little direct evidence that removal of specific substances from tobacco smoke or from tobacco actually reduces risk or harm to human health. In considering the health effects of modified tobacco products it is important to remember that the health consequences of the use of any such product are determined not by the toxic agents removed from the product but by the actual exposure to the toxins that remain. Harm reduction is the net difference in harm between the products as actually used.

There is strong evidence that in the range of exposures involved in smoking, there is a quantitative relationship between the magnitude of exposure and the incidence of cancer, coronary vascular disease, pulmonary disease, and several other tobacco-related illnesses. Rarely if ever is

there impartial and thorough assessment of the risk associated with new tobacco products relative to the risk of abstinence or the risk of other tobacco products prior to marketing. Unlike new tobacco products, nicotine replacement products are subject to full disclosure of content, rigorous testing, and the regulation of marketing claims by the of the Food and Drug Administration.

In addition to tobacco smoke, other forms of tobacco such as cigars, chewing tobacco, and snuff are also vectors of nicotine addiction and often have their own sets of serious toxic consequences.

The latent period between beginning exposure to tobacco and the development of most of the major adverse consequences is so long that empirical, direct evidence (assessment of immediate and long-term toxicity of individual tobacco products in humans) that one tobacco product is less harmful than another will rarely be available in time to be a basis for informing users. In the absence of direct evidence, conflicting claims of the degree of harm reduction are likely and informed usage decisions by smokers and nonsmokers will be difficult.

No one knows the dose-response relations, the specific toxins, the pathogenic mechanisms, or the interrelationship between the many components of tobacco smoke with enough precision to make scientifically reliable quantitative judgments about the risk or actual harm reduction associated with use of any tobacco product. Since we do not know which of many toxins may be the cause of specific harmful effects, we can only infer but we cannot know the health effects of the elimination of any one or several tobacco components. Further, we are just beginning to identify and understand the genetic basis and other causes of the differences in susceptibility to toxic effects among groups or individuals that largely determine the response of an individual to a toxin.

Nonetheless, it is reasonable to expect that some of the new products will reduce exposure to tobacco toxins and possibly reduce harm to some users and to others who are exposed to them. It is, therefore, urgent and important that the assessment of exposure to tobacco toxins resulting from the use of modified tobacco products or drugs be based on the best available evidence, made by the most qualified judges, and communicated to policy makers and the public completely and honestly.

There is little direct evidence available to serve as a basis for judgment as to the potential for harm reduction of specific new tobacco and pharmaceutical products. Therefore, any conclusions as to the relative harm of these products must necessarily be inferred from a base of indirect knowledge. The continuing introduction of new tobacco products with implicit or explicit claims of risk or harm reduction makes it important and urgent that the capacity for the best possible scientific assessment of these claims be put in place.

Since even the availability of harm reduction products may deter some from following the healthier course of abstinence or cessation, assessment of health claims should be based on an estimate of the effect of the product on the prevalence of smoking in the population, as well as the effect on the health risk to the individual smoker.

The most reliable scientific interpretation of necessarily incomplete indirect evidence comes when individuals who are experts in the relative fields, are not biased, and are free of conflict of interest form a consensual judgment. Such a judgment based on evidence of high quality should be a requirement for a conclusion that the use of a product is in fact associated with decreased exposure to toxins and that the decreased exposure is likely to be associated with less harmful outcomes.

Further, since these judgments of risk will necessarily be inferential because they are based on indirect and inconclusive evidence, some form of postmarketing surveillance of each product is important.

The charge to the committee is to address the science base for harm reduction from tobacco. The committee concluded early in its deliberations that the science base for harm reduction will evolve over time. There will inevitably be important interactions between the types of products that are developed and the science base. There will also be interactions between any regulatory process and the science base (the science base will influence regulation, and regulation will focus pertinent science) and, obviously, between regulations and products. For these reasons, the committee realized that the science base for harm reduction can be usefully considered only in the context of some sense of the types of specific products and of the consequences of regulation. Accordingly, portions of this report address both general categories of potential harm reduction products and regulatory considerations.

It is the strong sense of the committee that claims of less harm or risk associated with the use of tobacco products or drugs should be available—but only if four conditions are met: (1) There should be strong and widely available programs designed to avoid initiation and to achieve abstinence; (2) There should be premarketing evidence satisfactory to a group of disinterested experts that—as the product will actually be used by consumers—there is less exposure to toxic agents without coincidental increase in harm to the individual from other smoke components or to the population from encouraging initiation or continuation of smoking, the burden of proof of assertions of harm reduction should rest entirely with those making the assertion; (3) The public should be fully informed of the strength of the claims as assessed by an independent panel of experts. (4) There should be an effective surveillance system in place to determine short-term behavioral and the long-term health consequences of the use of the new products.

The committee wishes to express its great appreciation to the many individuals, listed in Appendix B, who contributed generously and substantially to it deliberations. Representatives of many health agencies as well as tobacco interests responded thoughtfully and extensively to the committee's questions.

Dr. Kathleen Stratton contributed perspective, insight, meticulous attention to detail, and essential oversight to the work and report. This report would not be possible without her substantial and important contributions.

Dr. Padma Shetty assumed responsibility for blocks of the report, and both the full report and many specific parts are testimony to her analytic, organizational, and expressive proficiency. Ann St. Claire organized the arrangements for the work of the committee with great finesse and also made useful contributions to the analytical work of the committee. Every member of the committee is deeply appreciative of the work of Dr. Stratton, Dr. Shetty, and Ms. St. Claire.

Stuart Bondurant
Chair

Contents

Executive Summary

BACKGROUND

Tobacco smoke is the cause of the most deadly epidemic of modern times. Smoking causes cancer (e.g., lung, oral cavity, esophagus, larynx, pancreas, bladder, kidney), chronic obstructive pulmonary disease (COPD), myocardial infarction, and stroke. The continuing toll of tobacco use has prompted the search for means of harm reduction for those who cannot or will not stop using tobacco. Numerous products that make implied or explicit claims to reduce the burden of smoking while allowing continued nicotine consumption are now entering the market. This report is concerned with the evaluation of these products.

Nearly one-quarter of adult Americans—an estimated 47 million people—smoke cigarettes (CDC, 2000a). Although this is far lower than the 42% recorded in 1965, the decline in the rates of smoking among adults appears to have leveled off during much of the 1990s (PHS, 2000). In a recent survey, 12.8% of middle-school children and 34.8 % of high school students reported some form of tobacco use during the month prior to their being interviewed (CDC, 2000b). The vast majority of smokers begin tobacco use during adolescence (IOM, 1994). However, 70% of smokers say they want to quit (CDC, 1994) and 34% of smokers make an attempt to quit each year. Thus, many but not all tobacco users find it very difficult to quit and continually expose themselves to known toxic agents.

DEFINITION OF HARM REDUCTION

For the purposes of this report, a product is harm-reducing if it lowers total tobacco-related mortality and morbidity even though use of that product may involve continued exposure to tobacco-related toxicants. Many different policy strategies may contribute to harm reduction. However, this report focuses on tobacco products that may be less harmful or on pharmaceutical preparations that may be used alone or concomitantly with decreased use of conventional tobacco. The committee does not use the term "safer cigarette," in particular, in order to avoid leaving the impression that any product currently known is "safe." Every known tobacco-containing product exposes the user to toxic agents; every pharmaceutical product can have adverse effects.

HISTORY OF EFFORTS TO REDUCE HARM FROM CIGARETTES

There have been many efforts in the past to develop less harmful cigarettes, none of which has proved to be successful. One of the first innovations with the promise of harm reduction was

the development of cigarettes with filters. Filters attempt to reduce the amount of toxicants that go into the smoke inhaled by the smoker. The next major modification of cigarettes with safety implications was "low-yield" cigarettes. These products emit lower tar, carbon monoxide (CO), and nicotine than other products as measured by the Federal Trade Commission (FTC) assay (the "smoking machine"). Many consumers believed, and still do, that these products pose less risk to health than other cigarettes.

However, data on the health impact of low-yield products are conflicting, in part due to a lack of systematic study early in the introduction of the products. Most current assessments of morbidity and mortality suggest that low-yield products are associated with far less health benefit, if any, than would be predicted based on estimates of reduced toxic exposure using FTC yields. In order to maintain the desired intake of nicotine, many smokers who changed to low-yield products also changed the way they smoked (e.g, compensated by inhaling more deeply than when smoking higher-yield products). Thus, their exposure to tobacco toxicants is higher than would have been predicted by standardized assays and people who have continued to use these products have not significantly reduced their disease risk by switching to them. Moreover, widespread use of these products might have increased harm to the population in the aggregate if tobacco users who might otherwise have quit did not, if former tobacco users resumed use, or if some people who would otherwise not have used tobacco did so because of perceptions that the risk with low-yield products was minimal.

TYPES OF EXPOSURE REDUCTION PRODUCTS

Tobacco and cigarette-like products have been introduced recently that, under measurement systems such as the FTC smoking machine, result in decreased emission of some toxicants compared to conventional tobacco products. Currently available products include tobacco with reportedly reduced levels of some carcinogens and cigarette-like products that deliver nicotine with less combustion than cigarettes. Two classes of pharmaceutical products approved by the Food and Drug Administration (FDA) for short-term use in smoking cessation might also be used for harm reduction. These include nicotine products, such as in patch, gum, inhaler, and nasal spray preparations, and a nonnicotine product that reduces the craving for tobacco. These cessation drugs could be used longterm to maintain cessation or concomitantly with continued but decreased use of conventional tobacco products (see Table 1).

These tobacco and pharmaceutical products could *potentially* result in reduced *exposure* to toxicants. The committee uses 'potentially', because whether exposure to tobacco toxicants is reduced depends on the user's behavior, such as frequency and intensity of use. Reduced exposure, however, does not necessarily assure reduced risk to the user or reduced harm to the population. Therefore, and in order to avoid misinterpretation, the committee uses the generic phrase "potential reduced-exposure products," or PREPs, when discussing the modified tobacco products, cigarette-like products (whether tobacco containing or not), or pharmaceutical products and medical devices (whether nicotine containing or not) used for their tobacco harm reduction potential. More such products are likely to be introduced in the near future, perhaps accompanied by claims that they are less harmful than conventional products.

Conclusion 5. *Regulation of all tobacco products, including conventional ones as recommended in IOM, 1994, as well as all other PREPs is a necessary precondition for assuring a scientific basis for judging the effects of using PREPs and for assuring that the health of the public is protected.* Regulation is needed to assure that adequate research (on everything from smoke chemistry and toxicology to long-term epidemiology) is conducted and to assure that the public has current, reliable information as to the risks and benefits of PREPs. Careful regulation of claims is needed to reduce misperception and misuse of the products. If a PREP is marketed with a claim that it reduces (or could reduce) the risk of a specific disease(s) compared to the risk of the product for which it substitutes, regulation is needed to assure that the claim is supported by scientifically sound evidence and that pertinent epidemiological data are collected to verify that claim.

Conclusion 6. *The public health impact of PREPs is unknown. They are potentially beneficial, but the net impact on population health could, in fact, be negative.* The effect on public health will depend upon the biological harm caused by these products and the individual and community behaviors with respect to their use. Regulation cannot assure that the availability of risk-reducing PREPs will lead to reduced tobacco-related harm in the population as a whole. However, a regulatory agency can assure that data are gathered that would permit the population effects to be monitored. If tobacco use increases or tobacco-related disease increases, these data would serve as a basis for developing and implementing appropriate public health interventions.

PRINCIPAL RECOMMENDATIONS

The committee believes that harm reduction is a feasible and justifiable public health policy – but only if it is implemented carefully to achieve the following objectives:

- Manufacturers have the necessary *incentive* to develop and market products that reduce exposure to tobacco toxicants and that have a reasonable prospect of reducing the risk of tobacco-related disease;
- Consumers are fully and accurately *informed* of all of the known, likely, and potential consequences of using these products;
- Promotion, advertising and labeling of these products are firmly *regulated* to prevent false or misleading claims, explicit or implicit;
- Health and behavioral effects of using PREPs are *monitored* on a continuing basis;
- Basic, clinical, and epidemiological *research* is conducted to establish their potential for harm reduction for individuals and populations, and.
- Harm reduction is implemented as a *component* of a comprehensive national tobacco control program that emphasizes abstinence-oriented prevention and treatment.

Recommendations about future research needs are based on Principal Conclusions 1-4 and can be found in the following section. They flow primarily from material presented in Section II of the report. Progress in these areas will permit the application of the principles of risk assessment to the evaluation of PREPs in the future. At present, judgement informed by incomplete science will be used to evaluate PREPs. However, immediate actions are required. Therefore, the committee makes recommendations that address Principal Conclusions 5 and 6. These conclusions and recommendations are particularly intertwined, requiring immediate attention and swift action.

The effect of PREPs could be to increase or decrease tobacco-related disease in the population. Assessing a positive public health impact will be difficult and will require extensive surveillance and research to ensure that the impact is positive. Even the strongest surveillance system could not alone provide minimal assurance of safety or protection of the public. Currently there is little public authority over tobacco products of any type. Whatever the current legal or regulatory posture with respect to these products, the committee realized that in order to obtain the best available scientific evaluation of emerging tobacco-related PREPs and to provide the best advice on use of all PREPs to the public, some national authority over these PREPs is needed. Only a comprehensive program of regulation and assessment including extensive premarket testing and surveillance offers a reasonable possibility of net gain in health from use of PREPs instead of conventional tobacco product use.

Therefore, the committee recommends development of a surveillance system to assess the impact of promotion and use of PREPs on the health of the public.

A national comprehensive surveillance system is urgently needed to collect information on a broad range of elements necessary to understand the population impact of tobacco products and PREPs, including attitudes, beliefs, product characteristics, product distribution/ and usage patterns, marketing messages such as harm reduction claims and advertising, the incidence of initiation and quitting and non-tobacco risk factors for tobacco-related conditions. There should be surveillance of major smoking-related diseases as well as construction of aggregate population health measures of the net impact of conventional product and PREPs.

The surveillance system should consist of mandatory, industry-furnished data on tobacco product constituents and population distribution and sales. Resources should be made available for a program of epidemiological studies that specifically address the health outcomes of PREPs and conventional tobacco products, built on a robust surveillance system and using all available basic and clinical scientific findings.

The committee further recommends strengthened federal regulation of all modified tobacco products with risk reduction or exposure reduction claims, explicit or implicit, and any other products offered to the public to promote reduction in or cessation of tobacco use. The committee outlines 11 principles to govern the regulation of PREPs. The regulation proposed by this committee is narrowly focused on assuring that the products reduce risk of disease to the user and accumulating data that would indicate whether or not the products are harm-reducing for the population in the aggregate. Other potential regulatory approaches to tobacco control are not addressed within this report.

The recommended regulatory structure builds on the foundation of existing food and drug law, with appropriate adaptations to take into account the unique history and toxicity of tobacco products. These principles envision testing and reporting for all tobacco products, approval of claims regarding reduced exposure and reduced risk regarding tobacco or cigarette-like products, and retention of current FDA regulation of pharmaceutical PREPs. Manufacturers of tobacco products and pharmaceuticals should be encouraged to develop and introduce new products that will reduce the burden of tobacco-related disease. The regulatory system proposed in this report is not to be viewed in isolation. It is proposed as an essential component of a package of public health initiatives (including research, education and surveillance) that this committee believes is necessary to realize whatever benefit tobacco and pharmaceutical product innovation can offer in reducing the nation's burden of tobacco-related illness and death. See Box 1.

Box 1 Regulatory Principles

Regulatory Principle 1. Manufacturers of tobacco products, whether conventional or modified, should be required to obtain quantitative analytical data on the ingredients of each of their products and to disclose such information to the regulatory agency.

Regulatory Principle 2. All tobacco products should be assessed for yields of nicotine and other tobacco toxicants according to a method that reflects actual circumstances of human consumption; when necessary to support claims, human exposure to various tobacco smoke constituents should be assessed using appropriate biomarkers. Accurate information regarding yield range and human exposure should be communicated to consumers in terms that are understandable and not misleading.

Regulatory Principle 3. Manufacturers of all PREPs should be required to conduct appropriate toxicological testing in preclinical laboratory and animal models as well as appropriate clinical testing in humans to support the health-related claims associated with each product and to disclose the results of such testing to the regulatory agency.

Regulatory Principle 4. Manufacturers should be permitted to market tobacco-related products with exposure-reduction or risk-reduction claims only after prior agency approval based on scientific evidence (a) that the product substantially reduces exposure to one or more tobacco toxicants and (b) if a risk reduction claim is made, that the product can reasonably be expected to reduce the risk of one or more specific diseases or other adverse health effects, as compared with whatever benchmark product the agency requires to be stated in the labeling. The "substantial reduction" in exposure should be sufficiently large that measurable reduction in morbidity and/or mortality (in subsequent clinical or epidemiological studies) would be anticipated, as judged by independent scientific experts.

Regulatory Principle 5. The labeling, advertising, and promotion of all tobacco-related products with exposure-reduction or risk-reduction claims must be carefully regulated under a "not false or misleading" standard with the burden of proof on the manufacturer, not the government. The agency should have the authority and resources to conduct its own surveys of consumer perceptions relating to these claims.

Regulatory Principle 6. The regulatory agency should be empowered to require manufacturers of all products marketed with claims of reduced risk of tobacco-related disease to conduct post-marketing surveillance and epidemiological studies as necessary to determine the short-term behavioral and long-term health consequences of using their products and to permit continuing review of the accuracy of their claims.

Regulatory Principle 7. In the absence of any claim of reduced exposure or reduced risk, manufacturers of tobacco products should be permitted to market new products or modify existing products without prior approval of the regulatory agency after informing the agency of the composition of the product and certifying that the product could not reasonably be expected to *increase* the risk of cancer, heart disease, pulmonary disease, adverse reproductive effects or other adverse health effects, compared to similar conventional tobacco products, as judged on the basis of the most current toxicological and epidemiological information.

Regulatory Principle 8. All added ingredients in tobacco products, including those already on the market, should be reported to the agency and subject to a comprehensive toxicological review.

Regulatory Principle 9. The regulatory agency should be empowered to set performance standards (e.g., maximum levels of contaminants; definitions of terms such as "low tar") for all tobacco products, whether conventional or modified, or for classes of products.

Regulatory Principle 10. The regulatory agency should have enforcement powers commensurate with its mission, including power to issue subpoenas.

Regulatory Principle 11. Exposure reduction claims for drugs that are supported by appropriate scientific and clinical evidence should be allowed by the FDA.

Research Conclusions and Recommendations

Many fruitful research directions should be explored to strengthen the scientific basis for assessing harm reduction. In reviewing the range of scientific disciplines and disease areas, the committee specifically noted five general scientific issues: (1) description of the dose–response relationship between tobacco smoke and/or constituent exposure and health outcomes, (2) identification and development of surrogate markers for disease, (3) the utility of pre-clinical research, (4) utility of short-term clinical and epidemiological studies, and (5) the role of long-term epidemiological studies and surveillance. The committee has reviewed the evidence available regarding these points and has described a research agenda to facilitate evaluation of the harm reduction potential of these products. This section summarizes the committee's conclusions and recommendations for future research, which are elaborated in detail in Section II of this report.

1. Currently available data allow estimation, albeit imprecise, of a dose–response relationship between exposure to whole tobacco smoke and major diseases that can be monitored for evaluation of harm reduction potential.

There are more than 4,000 different chemicals in tobacco smoke; many of these are known to be toxic. Many of the mechanisms of pathogenesis attributed to tobacco use have been explicated, and in a few cases, causative tobacco constituents have been identified. In order to effectively evaluate the toxic effects of tobacco smoke and identify the primary causal agents, the toxic components of PREPs and comparison products must be identified and be disclosed. For the most part, the data are insufficient to accurately describe the relationship of tobacco use and disease formation at the level of detail that would establish all causal agents involved or the exact dose–response relationship. The characteristics of this relationship vary among diseases and are affected by differences in compensation and actual exposure and by interindividual or population differences. Consequently, the confidence with which the adverse effects or harm reduction potential of PREPs can be extrapolated, especially at low doses, is uncertain. Also, there is currently no evidence to support a threshold level of tobacco exposure below which no risk exists for any of the reviewed health outcomes.

In summary, current knowledge of the dose–response relationships is sufficient to support risk reduction through exposure reduction as a goal for the individual through the use of these various products. To date, these relationships are not defined well enough in terms of specific components of smoke to serve as a predictive tool for the effect a particular product will have on most health outcomes. However, a strong quantitative relationship between maternal tobacco exposure and the incidence of spontaneous abortions and intrauterine growth retardation leading to low infant birthweight has been documented extensively. This population is one in which the actual health effects of PREPs and potential for harm reduction may be most directly evaluated. Further discussion regarding dose–response can be found in the disease-specific chapters in Section II (Chapters 12–16).

2. Although candidate disease-specific surrogate markers are currently available, further validation of these markers is needed. In addition, other biomarkers that accurately reflect mechanisms of disease must be developed to serve as intermediate indicators of disease and disease risk.

Table 1 Potential Reduced-Exposure Products

Category	Descriptors	Examples
Modified Tobacco	Reduced yield of selected toxicants	Advance™, low-nitrosamine tobacco cigarettes, Snus, reduced nitrosamine smokeless tobacco
Cigarette-like products	Less combustion than cigarettes	Premier™ (off market)
		Eclipse™
		Accord™
Pharmaceutical products	Nicotine Replacement	Nicotine gum, patches, inhaler, nasal spray
	Antidepressants	Bupropion SR, nortriptyline
	Other Medications	Nicotine antagonists, clonidine

THE COMMITTEE CHARGE AND ASSUMPTIONS

The Institute of Medicine (IOM) convened a committee of experts to formulate scientific methods and standards by which PREPs (pharmaceutical or tobacco-related) could be assessed. Four questions were imbedded within the charge given to the committee by the Food and Drug Administration (FDA) in December 1999. Where there are not yet answers, the committee was asked to outline the broad strategy by which the knowledge base might be assembled.

1. Does use of the product decrease exposure to the harmful substances in tobacco?
2. Is this decreased exposure associated with decreased harm to health?
3. Are there surrogate indicators of this effect on health that could be measured in a time frame sufficient for product evaluation?
4. What are the public health implications of tobacco harm reduction products?

The first three questions deal with the adequacy of current scientific methods to determine whether and to what extent these products reduce the risk of morbidity and mortality and the nature of the advice to give to citizens, health professionals, and others. The fourth question is important because it addresses the population impact of these products. That is, although a product might be risk-reducing for an individual's health compared to conventional tobacco products, its use might not be harm-reducing for the population as a whole. The fourth question is also important because the answer lays the groundwork for educational, policy, and regulatory actions.

The committee reviewed the literature and assessed the nature and availability of the data needed to evaluate the feasibility of tobacco harm reduction. Its review encompassed the major disease categories linked by scientific evidence to tobacco consumption, including cancer, cardiovascular disease, respiratory disease, reproductive and developmental disorders, and others. The report is offered to relevant federal and state regulatory and policy bodies, Congress, scientists and health care professionals, tobacco and pharmaceutical industries, and—most importantly—the public, who will have to decide whether or not to use these products.

The committee began with fundamental operating precepts, reiterating and reaffirming overwhelming scientific evidence and the conclusions of many scientific and policy advisory bodies:

Precept 1. Tobacco use causes serious harm to human health.

Precept 2. Nicotine is addictive.

Precept 3. The best means to protect individual and public health from tobacco harms are to achieve abstinence, prevent initiation and relapse, and eliminate environmental tobacco smoke exposure.

Precept 4. A comprehensive and authoritative national tobacco control program, with harm reduction as one component, is necessary to minimize adverse effects of tobacco.

PRINCIPAL CONCLUSIONS

The committee does not evaluate specific PREPs in this report, since the currently available tobacco-related PREPs in particular are most likely prototypes of limited life span. Under present regulatory conditions, tobacco-related PREPs can be changed with little assessment and without disclosure of their contents. Therefore, the committee considered the types of PREPs currently or likely to become available in the foreseeable future. After reviewing a large body of scientific documents and data, hearing presentations from many scientific, regulatory and industrial interests, and publicly soliciting comments on the issues at hand, the committee reaches the following principal conclusions regarding the questions posed by the charge:

Conclusion 1. *For many diseases attributable to tobacco use, reducing risk of disease by reducing exposure to tobacco toxicants is feasible.* This conclusion is based on studies demonstrating that for many diseases, reducing tobacco smoke exposure can result in decreased disease incidence with complete abstinence providing the greatest benefit.

Conclusion 2. *PREPs have not yet been evaluated comprehensively enough (including for a sufficient time) to provide a scientific basis for concluding that they are associated with a reduced risk of disease compared to conventional tobacco use.* One narrow exception is the use of nicotine gum in one study for maintenance of cessation, described in Chapters 8, 13, and 14. Carefully and appropriately conducted clinical and epidemiological studies could demonstrate an effect on health. However, the impact of *PREPs* on the incidence of most tobacco-related diseases will not be directly or conclusively demonstrated for many years.

Conclusion 3. *Surrogate biological markers that are associated with tobacco-related diseases could be used to offer guidance as to whether or not PREPs are likely to be risk-reducing.* However, these markers must be validated as robust predictors of disease occurrence, and should be able to predict the range of important and common conditions associated with conventional tobacco products. Furthermore, the efficacy of PREPS will likely depend on user population characteristics; e.g. those defined by gender, genetic susceptibility, ethnicity, tobacco history, and medical history.

Conclusion 4. *Currently available PREPs have been or could be demonstrated to reduce exposure to some of the toxicants in most conventional tobacco products.* Many techniques exist to assess exposure reduction, but the report contains many caveats about the use of all of them, including usually an unknown predictive power for harm.

Biomarkers are measurements of any tobacco constituent, tobacco smoke constituent, or effect of such a compound in a body fluid (including exhaled air) or organ. Although some biomarkers currently exist, these require further validation and more must be developed that have adequate sensitivity, specificity, and limited complexity and that quantitatively link biological exposure of tobacco smoke or specific constituents to disease induction or progression prior to the advent of clinically apparent disease. Validation and development of biomarkers will provide a stronger foundation by which to make scientific evaluations and regulatory decisions regarding PREPs.

Although no panel of markers can be utilized currently to evaluate the health effects of PREP use, potential biomarkers have been and are being developed for many of the relevant disease categories. The committee recommends further study of biomarkers for various disease categories that may potentially be determined to be intermediate indicators of disease and disease risk. For example, possible measures include markers of platelet and vascular activation, lipid peroxidation, and inflammation, which have the potential to be related to measures of cardiovascular physiology and, ultimately, reflect the risk of clinical cardiovascular disease as well as markers of inflammation in lung disease. Also, biomarkers of cancer that may indicate early carcinogenic processes and risk of cancer development include but are not limited to markers of genetic damage in blood, sputum, urine, and internal organs. Another potential marker is the measurement of bone density as a direct reflection of the severity and risk of osteoporosis.

Ideally, a set of behavioral markers is needed to monitor product use patterns, thereby enabling clinicians and researchers to measure substitution of PREP use for cessation. Although the committee realizes the difficulty of developing a set of such behavioral markers, they are needed for a comprehensive evaluation of PREPs. A further detailed research strategy regarding the development of biomarkers can be found in the disease-specific chapters (Chapters 12–16) and the chapter on exposure and biomarkers assessment (Chapter 11).

3. *The evaluation of PREPs will be facilitated by the development of appropriate animal models and in vitro assays of the pathogenesis of tobacco-attributable diseases.*

Animal models and in vitro testing can contribute to the evaluation of individual PREPs and to the development of a scientific basis for designing and evaluating harm reduction products. Such studies could include cell culture, animal studies, and molecular studies to document specific toxicants as the most likely causative agents, to better define pathogenic effects of tobacco smoke exposure, to better explain the relationship of disease risk regression and exposure regression (dose–response relationships), and to validate biomarkers of exposure and biological effect.

The new technologies of genomics and proteomics have the potential for evaluating and comparing the effects of tobacco exposure and PREP use on gene translation and expression in neoplastic and nonneoplastic disease.

The committee recommends specific applications of pre-clinical models for specific tobacco-attributable disease. For example, the committee recommends the utilization of genomic and proteomic technologies to investigate the effect on gene translation and expression of tobacco smoke exposure and its relevance for pulmonary, cardiovascular and neoplastic health outcomes. Also, accurate models are needed for smoke or tobacco constituent exposure (including nicotine) and exposure to PREPs and their effects on the development of COPD, cardiovascular disease, neoplasia, and in utero injury. Again, a more detailed pre-clinical research agenda can be found in the disease-specific chapters in Section II (Chapter 12–16).

4. *Short-term clinical and epidemiological studies in humans are required for the comprehensive evaluation of PREPs.*

Some effects of PREPs in humans could be evaluated by epidemiological studies, by measurement of intermediate disease markers or, in some cases, by clinical studies of smokers who are unwilling or unable to quit but are willing to use PREPs (compared to a control group of conventional tobacco product users). The committee recommends the utilization of validated intermediate biomarkers of disease effect in these studies in order to assess potential harm reduction within a practical time frame for diseases that occur only after prolonged exposure. Examples of potential measures include the use of lung function tests or inflammatory changes, evaluated through bronchoalveolar lavage, as intermediate markers for COPD in interventional studies.

A few smoking-attributable diseases develop after relatively brief exposure (weeks to months) and provide an opportunity for strong short-term clinical and epidemiological studies. These diseases include intrauterine growth retardation leading to low infant birthweight, slowed wound or ulcer healing, and perhaps acute myocardial infarction. Human studies are also required for evaluating the relationship of individual smoking history, environment, gender, race, and other factors (e.g., diet) to disease risk and susceptibility. Further discussion regarding the utilization of clinical studies can be found in Section II (Chapters 12–16).

5. *Long-term epidemiological studies of populations and/or pilot groups of users should monitor the incidence of disease or other adverse effects.*

Most tobacco-related diseases develop clinically over many years, and the only direct and definitive way to evaluate the harm reduction value of PREPs is to monitor the health outcomes of users compared to appropriate control groups over an extended period of time. Such surveillance could be an add-on to other epidemiological studies and should include ongoing reports of smoking behavior, types of products used, and health outcomes, as well as intermittent collection of biological samples for biomarker assessment in a segment of users. Further discussion can be found in Chapter 6 and in the disease-specific chapters in Section II (Chapters 12–16).

Risk Assessment

A report published in 1983 by a committee of the National Research Council outlined important steps and considerations in risk assessment (NRC, 1983). The "Red Book" identified important steps: hazard identification (Does the toxicant cause the adverse effect?), dose-response assessment (What is the relationship between dose and incidence in humans?), exposure assessment (What exposures are currently experienced or anticipated under difference circumstances?), and risk characterization (What is the estimated incidence of the adverse effect in a given population?). A risk characterization provides important information for risk management, which also includes public health, social, economic, and political considerations.

The committee did not do a formal risk assessment of PREPs. The knowledge base is inadequate to do so at this time. However, the "Red Book" framework has great utility in presenting the committee's work. Table 2 uses it to summarize material discussed in Chapters 1, 5, 6, 7 and 8. Even though the committee has concluded that harm reduction through the use of PREPs is not yet convincingly demonstrated, Table 2 illustrates how the committee's conclusions and recommendations are key to gathering important data. This new knowledge base will permit a more definitive evaluation of harm reduction as a strategy and of PREPs as tools for reducing tobacco-related morbidity and mortality.

Based on an extensive review of the scientific and medical literature, the committee concludes that although harm reduction is feasible, no currently available PREPs have been shown to be associated with biologically relevant exposure reduction or with decreased tobacco-related harm. One narrow exception is the use of nicotine gum in one study for maintenance of cessation, described in Chapters 8, 13, and 14. Without a comprehensive program of scientific research, surveillance, and regulation, the potential benefit of harm reduction will go unrealized. Furthermore, without such a comprehensive program PREPs could, in fact, be detrimental to both individual and public health.

Table 2 Use of Risk Assessment Framework in Assessing Tobacco Harm Reduction

	Hazard Identification	Dose Response	Exposure Assessment	Risk Characterization	Risk Management
Information required as described in 1983 "Red Book"	Epidemiology Animal Bioassay Short term Studies Comparisons of Molecular Structure	Epidemiology Low-dose extrapolation Animal to human extrapolation	Dose to which humans are exposed Dose of special populations Estimation of size of population potentially exposed	Estimate of the magnitude of the public health problem.	A risk-assessment (qualitative or quantitative) may be one of the bases of risk management
Challenges in Risk Assessment of Conventional Tobacco Products	Complex mixture Animal models are limited Constituents and additives are proprietary information	Dose changes for an individual over time Dose of individual toxicants varies over time Exposure at time of disease progression	Changes in smoking topography Complex mixture	For which disease? At which point in smoking history?	FTC regarding advertising
Additional challenges of PREP Risk Assessment	Tobacco-related products will change rapidly with time	Assessing effect of moving backwards on a dose-exposure curve, assuming long-time previous higher exposure	Changing exposure after long-term higher dose exposure Some toxicants could increase	Need models to consider effects on initiation, cessation, and relapse	FDA authority currently exerted only over pharmaceutical PREPs
Committee Charge	1. Does product decrease exposure to the **harmful substances** in or produced during use of tobacco?	2. Is decreased exposure associated with decreased harm to health? 3. Are there useful surrogate indicators of disease that could be used?	1. Does product **decrease exposure**?	4. What are the public health implications?	4. What are the public health implications?
Disease-specific Summary Data (Chapter 5; Section II)	3.Utility of preclinical research to judge feasibility	1.Dose-response data for conventional tobacco products 2.Validation and development of biomarkers 4.Short-term clinical and epidemiological studies	2.Validation and development of biomarkers 4.Short-term clinical and epidemiological studies	5. Long-term epidemiological studies and surveillance	
Principal Conclusions	1. Risk reduction is feasible 4. Exposure reduction can be demonstrated.	3. Surrogate measures could be used to predict risk reduction	4. Exposure reduction can be demonstrated	1. Risk reduction is feasible 2. Risk reduction not yet demonstrated 6. Public health impact is unknown	5. Regulation is a necessary precondtion for asuring a science base and for assuring protection of the health of the public
Elements of surveillance system	Specific tobacco constituents of both the products and the smoke they generate	Disease outcomes	Consumption of tobacco products and of PREPs Biomarkers of exposure to tobacco products Personal tobacco product use and related behavioral patterns	Disease outcomes	Tobacco product marketing, including PREPs

	Hazard Identification	Dose Response	Exposure Assessment	Risk Characterization	Risk Management
Regulatory Principle **(all refer to tobacco-related PREPS, except for 11)**	1. Ingredient disclosure 3. Preclinical testing required to support health-related claims 7. Evidence for no increased risk 8. Added ingredient review 9. Performance Standards	6. Products with claims would require post-marketing surveillance and epidemiological studies	2. Yield Assessment 4. With specific claims, no increased exposure to unclaimed compounds 9. Performance Standards 11. Exposure reduction claims for pharmaceutical PREPs	5.Labeling for products with claims cannot be false or misleading	10. Enforcement power
Recommendation	3. Develop appropriate animal models and in vitro assays of pathogenesis	1. Sufficient data to allow estimation of D-R 2. Need to develop validated biomarkers of disease	4. Clinical and epidemiological studies in human are required	Comprehensive surveillance is recommended	Regulation is recommended

REFERENCES

CDC (Centers for Disease Control and Prevention). 1994. Health Objective for the Nation Cigarette Smoking Among Adults–United States, 1993. *Morbidity and Mortality Weekly Report* 43(50):925-930.

CDC (Centers for Disease Control and Prevention). 2000a. Cigarette Smoking Among Adults–United States, 1998. *Morbidity and Mortality Weekly Report* 49(39): 881-884.

CDC (Centers for Disease Control and Prevention). 2000b. Tobacco Use Among Middle and High School Students–United States, 1999. *Morbidity and Mortality Weekly Report* 49(3): 49-53.

IOM (Institute of Medicine). 1994. *Growing Up Tobacco Free*. Lynch, B.S., and R.J. Bonnie, Eds. Washington, DC: National Academy Press.

NRC (National Research Council). 1983. *Risk Assessment in the Federal Government: Managing the Process*. Washington, DC: National Academy Press.

PHS (Public Health Service). 2000. Health, United States, 2000 With Adolescent Health Chartbook. Hyattsville, MD: National Center for Health Statistics.